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TITLE: Mechanistic Links Between PARP, NAD, and Brain Inflammation After TBI

PRINCIPAL INVESTIGATOR: Raymond A. Swanson, M.D

CONTRACTING ORGANIZATION: Northern California Institute for Research & Education

San Francisco, CA 94121

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6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

NCIRE
151NC, 4150 Clement St.
San Francisco, CA 94121

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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This project is a pre-clinical evaluation of the efficacy of veliparib and NAD as agents for suppressing inflammation and improving outcomes after traumatic brain injury. The animal models include pig and rat models of controlled cortical impact and blast injury. Work completed in this year 2 (of 3) includes the large majority of the pig CCI and blast studies, and all rat veliparib animal surgeries. The behavioral analyses for these is completed, and the histological analyses are ongoing. Rat blast studies are ongoing. The studies using NAD as an anti-inflammatory agent have also been initiated. Results of the studies completed confirm that veliparib and NAD attenuate microglial activation after both blast and CCI. Veliparib improves outcome on some of the elevated plus maze and several aspects of the 5-choice reaction test when administered within 2 hours of injury. Analysis of long term (2-month) survival is ongoing.
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15. SUBJECT TERMS
brain injury, blast injury, rat, pig, inflammation, metabolism, microglia

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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Table of Contents

Page

1. INTRODUCTION

This is a pre-clinical study to establish the effectiveness of two anti-inflammatory approaches in improving recovery after traumatic brain injury. The studies employ rats and pigs, and use blast injury and controlled cortical injury (CCI) models. The underlying rationale for these studies is based on the salutary effects of ketogenic diet, which acts in part by suppressing brain inflammatory responses. Here we aim to suppress inflammation with (a) veliparib (an inhibitor of poly(ADP-ribose) polymerase, which acts by suppressing NF-kB – mediated inflammatory responses; and (b) intranasal NAD, a natural metabolite which we have in prior studies shown to also suppress poly(ADP-ribose) polymerase activity and inflammatory responses. CtBP1/2 knockout mice will be generated to test a specific mechanism by which ketogenic diet could may have anti-inflammatory effects. For all studies, outcome measures include histological indices of inflammation, cell death, and axonal injury, with behavioral indices of motor coordination, cognitive function, and anxiety. Some studies also use electrocorticography measures of brain network activity.

2. KEYWORDS

brain injury, blast injury, mouse, rat, pig, electrocorticography, inflammation, metabolism, microglia, ketogenic diet

3. ACCOMPLISHMENTS

What were the major goals of the project?

From the SOW:

Year 1

a) Establish blast injury models for rats and swine.
Status: Completed.

b) Initiate blast injury studies in rats and swine
Status: Completed

c1) In rats, establish the dose and time window of opportunity' for treatment with a PARP inhibitor (veliparib).
Status: Surgery and behavioral outcome studies completed (see Appendix D, E, and F); analysis of histological data is ongoing

c2) In rats, establish the 'time window of opportunity' for treatment with intranasal NAD .
Status: Analysis of histological outcomes at the early time point (15 minutes) is ongoing. Studies at later time points have not yet been initiated.

d) In pigs, establish the time window of opportunity for treatment with a PARP inhibitor.
Status: Completed (though this aim was truncated to histological analysis at a single time point as described previously.)

Year-2:
a1) In rats, establish the efficacy and 'time window of opportunity' for veliparib treatment after blast injury, using histological and behavioral outcome measures
Status: Behavioral analysis at the early time point is completed (see Appendix E)

a2) In rats, establish the efficacy and 'time window of opportunity' for NAD treatment after blast injury, using histological and behavioral outcome measures
Status Histological analysis at the earlier time point is ongoing.

b) In pigs, establish the efficacy and 'time window of opportunity' for veliparib treatment after blast injury, using histological and behavioral outcome measures.
Status: Completed (blast injury produced no consistent histological injury)

c) In rats, identify the electrophysiological changes in motor circuit function after CCI during over the acute and recovery periods using cortical and depth electrode arrays.
Status: Studies are ongoing

d) Using a CtBP1/2 transgenic mouse, test the hypothesis that effects of a ketogenic diet can be replicated by inhibiting CtBP dimerization.
Status: There have been problems in generating the mouse (see below). We have proof of principle for this idea using a peptide inhibitor.

What opportunities for training and professional development has the project provided?
1. Two members of the research team attended the 2015 California Neurotrauma symposium (Won and Bishop)
2. Three members of the research team attended the Society for Neuroscience Meeting and presented the work described here (Swanson, Won, and Irvine)
3. The P.I. was a participant in the Dept. of Veterans Affairs State of the Art conference on traumatic brain injury .

How were the results disseminated to communities of interest?
1.) Poster presentation at the 2015 Society for Neuroscience Meeting (see appendix)

What do you plan to do during the next reporting period to accomplish the goals?
Studies will proceed as described in the award proposal/SOW. In particular, we will proceed to studies involving behavioral outcome measures and the electrocorticography measures, and studies with the CtBP mouse.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
Nothing to Report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change.

1. Pig behavioral studies – showed no behavioral deficits after either blast or CCI. Our evaluations included a novel object recognition task, a hurdle crossing tasks, and a video analysis of gait. Discussion of this issue with other researchers in the field identifies this as a major limitation with use of pigs in general, stemming from their proclivities as herd animals, lack of digits, and small numbers available for any given experiment. We have discontinued the pig behavioral experiments and will use only histological outcome measures from the pigs.

2. Rat blast model - showed little blast-induced injury when the head is fully immobilized. There was a reproducible signal on some of the behavioral studies, which is interesting in itself, but as a criteria for evaluation of NAD and veliparib this is insufficient. We have revised the blast studies to allow reproducible head movement in one direction. This is thus a more complex model – involving both blast and closed head trauma – but it is on the other hand much more realistic that a "pure" blast exposure.

3. Constructs for generating conditional CtBP2$^{-/-}$ mice are were sequenced and found to be correct, but 2 attempts at generating ES cells from these constructs failed. We have therefore proceeded with the new TALENS system for generating the mice.

Changes that had a significant impact on expenditures. None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents. None

Significant changes in use or care of human subjects. N/A

Significant changes in use or care of vertebrate animals. None

Significant changes in use of biohazards and/or select agents. N/A

6. PRODUCTS

Journal & book publications. None

Other publications, conference papers, and presentations.
See Appendix C. Presentation at 2015 Society for Neuroscience meeting

Website(s) or other Internet site(s). None.

Technologies or techniques. None.

Inventions, patent applications, and/or licenses. None

Other Products. None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Raymond A. Swanson MD
Project Role:	PI
Researcher Identifier	ORCID 0000-0002-3664-5359
Nearest person month worked	2.4
Contribution to project	Study design, personnel recruitment, compliance, data analysis
Funding support	This award

Name:	S. Scott Panter PhD
Project Role:	Faculty
Researcher Identifier	
Nearest person month worked	1.0
Contribution to project	Supervision of all studies done with pigs
Funding support	This award, Dept. of Veterans Affairs

Name:	Karunesh Ganguly, MD, PhD
Project Role:	Faculty
Researcher Identifier	
Nearest person month worked	1.5
Contribution to project	Mouse electrocorticography studies
Funding support	Dept. Veterans Affairs

Name:	Valerie Coppes
Project Role:	Large animal surgery technician
Researcher Identifier	

Nearest person month worked	3.0
Contribution to project	Conducted pig TBI and histology
Funding support	Dept. Veterans Affairs

Name:	David Kapfhamer, PhD
Project Role:	Research Scientist
Researcher Identifier	
Nearest person month worked	8.0
Contribution to project	Rat histology and behavioral assessments
Funding support	This award

Name:	Katherine Hamel
Project Role:	Large animal surgery technician
Researcher Identifier	
Nearest person month worked	6
Contribution to project	Pig TBI, post-op monitoring, and histology
Funding support	This award

Name:	Seok Joon Won, Robin Bishop, PhD
Project Role:	Research Scientist
Researcher Identifier	
Nearest person month worked	9.0
Contribution to project	
Funding support	This award

Name:	Karen-Amanda Irvine, PhD
Project Role:	Research Scientist
Researcher Identifier	
Nearest person month worked	12.0
Contribution to project	Rat behavioral studies and rat brain histology
Funding support	This award

Name:	Robin Bishop, MS
Project Role:	Technician / Lab supervisor
Researcher Identifier	
Nearest person month worked	9.0

Contribution to project	Purchasing, stocking, coordinates studies, assists in behavioral assessments, conducts rat blast injury experiments.
Funding support	This award

Change in active other support of the PD/PIs or senior /key personnel
Dr. Panter has retired due to health reasons and as of May 2015 is no longer receiving support through this grant. Support to Valerie Coppes, Katherine Hamel, has also ended, and support to David Kapfhamer will end 11/15/15.

What other organizations were involved as partners?
None

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

Appendix A. Updated Quad Chart
Appendix B. Presentation at University of California Traumatic Brain Injury conference
Appendix C. Presentation at 2015 Society for Neuroscience meeting
Appendix D. Rat behavioral data summaries
Appendix E. Dose response veliparib summary
Appendix F. Gene expression changes after rat CCI

APPENDIX A

Mechanistic Links between PARP, NAD, and Brain Inflammation after TBI

Log Number 13306001
Award Number W81XWH-13-2-0091

PI: Raymond A. Swanson, M.D. **Org:** Northern California Institute for Research and Education **Award Amount:** $1,979,662

Study/Product Aim(s)

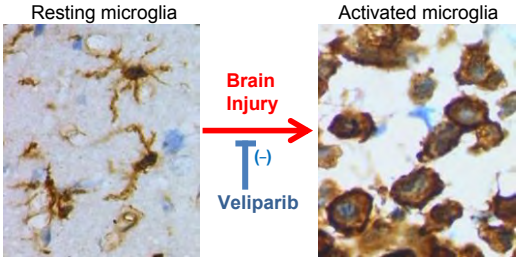
Objective: Establish a validated treatment approach for TBI, targeting brain inflammation, that can be implemented hours-to-days after injury.

Aims:

- Evaluate functional and histological markers of focal injury and diffuse axonal injury.
- Evaluate the effects of a PARP inhibitor (veliparib) on these endpoints
- Evaluate delayed intranasal administration of NAD on these endpoints
- Test the hypothesis that the effects of intranasal NAD and ketogenic diet on TBI are each mediated through actions of the NAD-sensitive transcription factor, CtBP, on inflammatory pathways.

Approach

Studies employ two TBI models: blast injury and controlled cortical impact, and 2 species, rat and pig. Animals are treated post-injury with veliparib or NAD, and subsequently assessed by behavioral tests (for anxiety, learning, and motor function) and histological measures (for inflammation, cell death, and axonal injury).



Accomplishment: Veliparip 3 mg/kg/d was shown to completely suppress microglial activation after TBI, in both rats and pigs.

Timeline and Cost

Activities CY	13	14	15	16
Establish the TBI models & histological and behavioral outcomes				
Evaluate veliparib in these models				
Evaluate NAD in these models				
Identify e-phys correlates of recovery and drug effects				
Generate CtBP1/2 ko mouse				
Estimated Budget ($K)	238	635	635	475

Updated: October 24, 2015

Goals/Milestones

CY13 Goal – Equipment acquisition, personnel hires, and approvals
☑ All in place

CY14 Goals – Model characterizations (behavioral and histological)
☑ Rat CCI ☑ Rat blast ☑ Pig CCI ☑ Pig blast
☑ Dose / response of veliparib on brain inflammatory response

CY15 Goal – Establish veliparib efficacy at delayed time points after TBI
☑ Rat CCI ☐Rat blast

CY16 Goals – Establish NAD efficacy at delayed time points after TBI
☑ Dose / response of NAD on brain inflammatory response
☐ Evaluate e-phys effects of veliparib & NAD
☐ Evaluate CtBP-/- genotype on TBI outcomes

Comments/Challenges/Issues/Concerns

- •. CtBP ko mouse still in production
- Behavioral studies in the pig are not feasible

Budget Expenditure to Date
Projected Expenditure: $1,508,000
Actual Expenditure: $1,668,355

APPENDIX B

Oral Presentation to 2014 University of California Brain Trauma meeting

True Blast injury – Fact or Fiction?

DoD- funded project to evaluate effectiveness of using a PARP inhibitor (veliparib) to suppress brain inflammation after TBI in multiple preclinical models:

CCI and blast injury in rats (Raymond Swanson, Robin Bishop, Seok Joon Won)

CCI and blast injury in swine (Scott Panter, Valerie Coppes, Katie Hamel, Preeti Mann)

Blast exposure (e.g. land mine, or mortar shell) --> multiple mechanisms of brain injury

- Skull penetration
- Brain deformation due to rapid acceleration/deceleration
- Brain vs. skull collision
- Intrinsic effects of a blast wave on axons, capillaries, etc.

Does this mechanism in fact contribute to brain injury?

The technical, experimental issue:

Experimental blast exposure also causes head movement / skull deformation.

This study:

Compare histologic outcomes after blast exposure to rats with some head movement vs. "no" head movement.

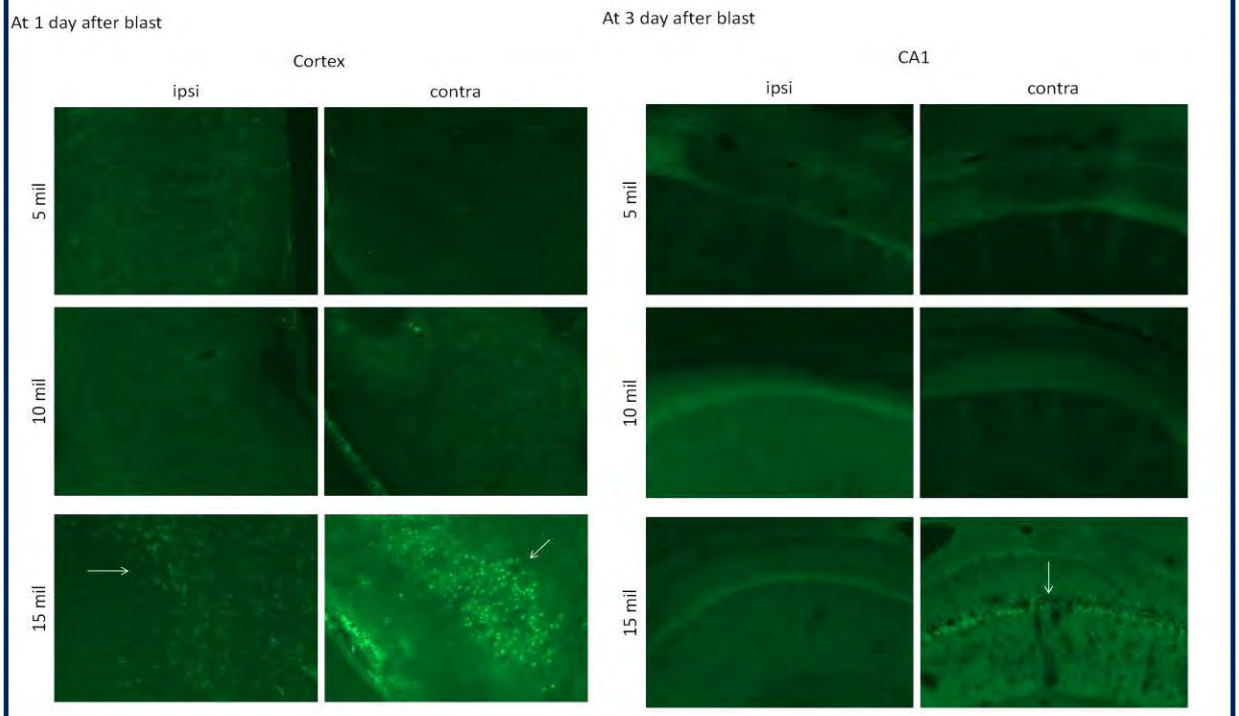
Blast Tube setup
(L-3/Jaycor)

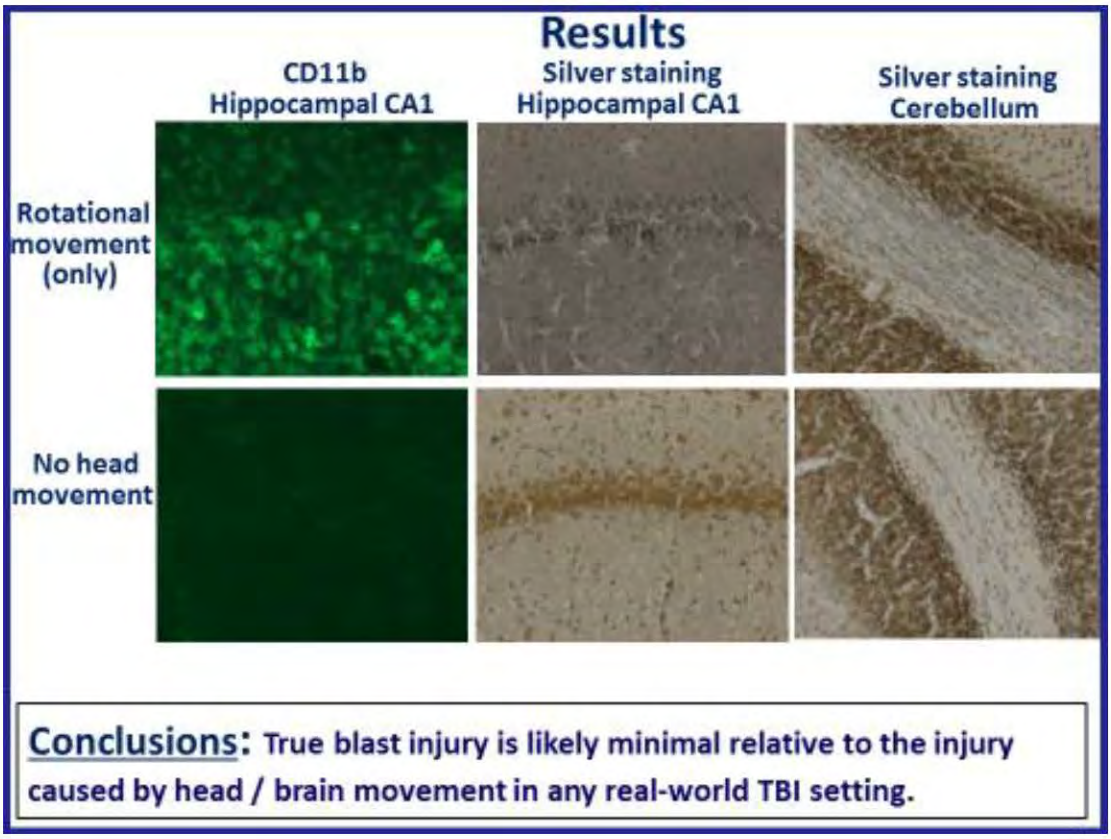
Peak pressure = 220 psi pressure
Positive pressure duration = 2.6 msec

Rotational movement (only)

No head movement

Examples of neuronal injury induced by 3 different grades of blast injury in cortex (left) and hippocampus (right). The highest grade, 15 mil, corresponds to 200 psi overpressure. Dead neurons are stained bright green by fluoro-jade B





APPENDIX C

University of California San Francisco

Veliparib suppresses microglial activation after brain trauma in rats and pigs

K-A. IRVINE, J. XU, R. K. BISHOP, P. SINGH, A. SONDAG, K. HAMEL, V. COPPES, D. J. KAPFHAMER, S. WON, S. PANTER, R. A. SWANSON

Introduction

Traumatic brain injury (TBI) is a major cause of long-term disability in industrialized and developing countries across the world (Hyder 2007). TBI leads to tissue disruption and release of molecules from injured and dead cells that elicit microglial activation and infiltration of circulating immune cells. These cells in turn release factors with cytotoxic effects (i.e. cytokines) that can increase secondary injury and impair recovery. We have shown previously that treatment with a PARP inhibitor, INO-1001, for 12 days after TBI, with the first dose given as long as 20 hrs after injury, can reduce inflammation and improve histological and functional outcomes (d'Avila 2012). PARP-1 (poly(ADP-ribose) polymerase-1) is an enzyme involved in both DNA repair and transcriptional regulation, which is activated by DNA damage and by cytokines such as TNFα. Inhibition of PARP-1 has been shown to suppress NF-κB dependent gene transcription in microglia and prevent their morphological transformation, proliferation and migration to injury sites.

In this study we evaluate the anti-inflammatory effect of the PARP-1 inhibitor, **Veliparib**, following cortical controlled impact (CCI) in rats and pigs.

Figure 1: *Doses of veliparib at and above 1mg/kg markedly suppress microglial activation as assessed by Iba-1 positive cell intensity in rats and pigs 7 days post-injury.*

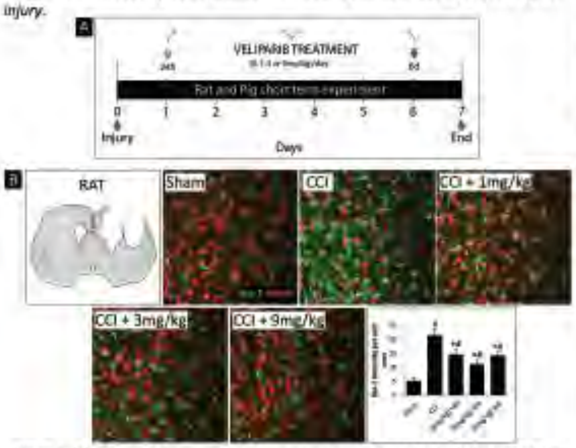


Figure 1: **(A)** Schematic diagram of the experimental protocol used in both the rat and pig studies. **(B)** Representative images of the striatum immunolabeled with the microglia/macrophage marker, Iba-1 and neuronal marker, NeuN from sham, CCI, and veliparib treated rats. Graph depicts quantification of images in **B**. * - vs CCI group (P = <0.05). # - vs Sham group (P = <0.05).

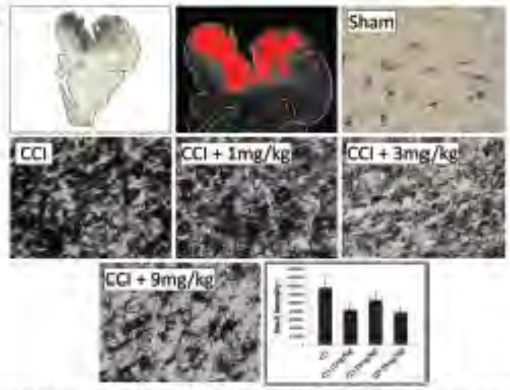


Figure 1: **(C)** Representative images from the perilesion border (red) immunolabeled with the microglia / macrophage marker, Iba-1 (black) from sham, CCI, and veliparib treated pigs. Graph depicts quantification of images in **C**.

Figure 2: *Doses of veliparib of 3mg/kg reduce the mRNA expression of Matrix metalloproteinase 9 (MMP-9) and Gp91 as assessed RT-PCR 3 days post-injury.*

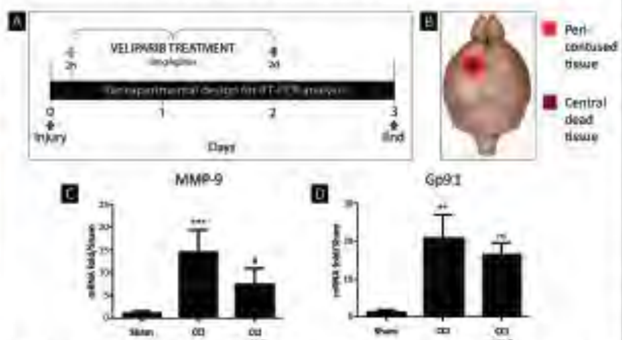


Figure 2: **(A)** Schematic diagram of the experimental protocol used in a short term study assessing the effect of [3mg/kg] of veliparib on the mRNA expression of the proinflammatory markers, MMP-9 and Gp91 3 days post-injury. **(B)** Tissue for analysis was taken using a "biopunch" to excise the perilesional border. **(C - D)** Transcript levels of MMP-9 and Gp91 from each condition revealed that veliparib reduced expression of Gp91 and significantly reduced the expression of MMP-9 when compared to untreated rats. *** - vs sham group (P = <0.001), ** - vs Sham group (P = <0.01) and # - vs CCI group (P = <0.01).

Figure 3: *Preliminary behavioral studies indicate a beneficial effect of Veliparib on functional outcome that is dependent on timing of drug treatment.*

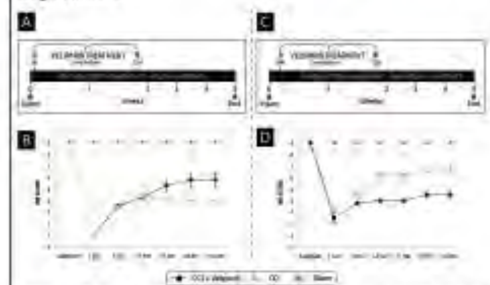


Figure 3: **(A and C)** Schematic diagrams of the experimental protocols used in the two long term studies assessing the effect veliparib [3mg/kg] on the extent of behavioral recovery following TBI. Veliparib treatment was started at 2 hours **(A)** or 24 hours **(C)** post injury. Recovery forelimb function was assessed using the IBB forelimb scale. **(B)** When veliparib was given acutely (2 hr) the rats recovered a greater extent of forelimb function than untreated rats. If the veliparib treatment is delayed, and started at 24 hours, then the extent of forelimb recovery was actually impaired when compared to untreated rats **(D)**. Supporting this, ANOVA revealed a significant timing by drug condition interaction. $F(1,11) = 6.04$, $p < 0.05$

General Methods

Rats

Dose response study: 25 Long Evans males (250 - 300g); 5 groups (Sham (n=5), 0mg/kg (n=5), 1mg/kg (n=5), 3mg/kg (n=5) and 9mg/kg (n=5)). RT-PCR study: 17 Long Evans males (250 - 300 g); 3 groups (Sham (n=5), 0mg/kg (n=6), and 3mg/kg (n=6)). Behavioural Studies: 22 Long Evans males (250 - 300 g); 3 groups (Sham (n=7), 0mg/kg (n=7), and 3mg/kg (n=8)). Veliparib given i.p.

INJURY: CCIs were centered over the forelimb sensorimotor cortex ([illegible] medial-lateral; [illegible] anterior-posterior). The injury was produced using the PCI 3000 (Hatteras Instruments Inc, NC) device with a 4mm impactor tip, at a velocity of 1.5 m/second and dwell time of 120 ms.
BEHAVIOR: IBB forelimb scale (Irvine et al., 2010 and 2014)
HISTOLOGY: Iba-1 (Abcam) and NeuN (Millipore) immunohistochemistry.
RT-PCR: Total RNA was extracted from the peri-contused tissue. The MMP-9, Gp91 and GAPDH primers were designed according to Pubmed GenBank and synthesized by Eurofins Genomics. Transcript levels of all genes from each sample were normalized to its GAPDH mRNA level using 2−ΔΔCT method.
ANALYSIS/STATISTICS: Iba-1 signal intensity assessed using ImageJ. One-Way ANOVA with Dunnetts post hoc test when appropriate.

Pigs

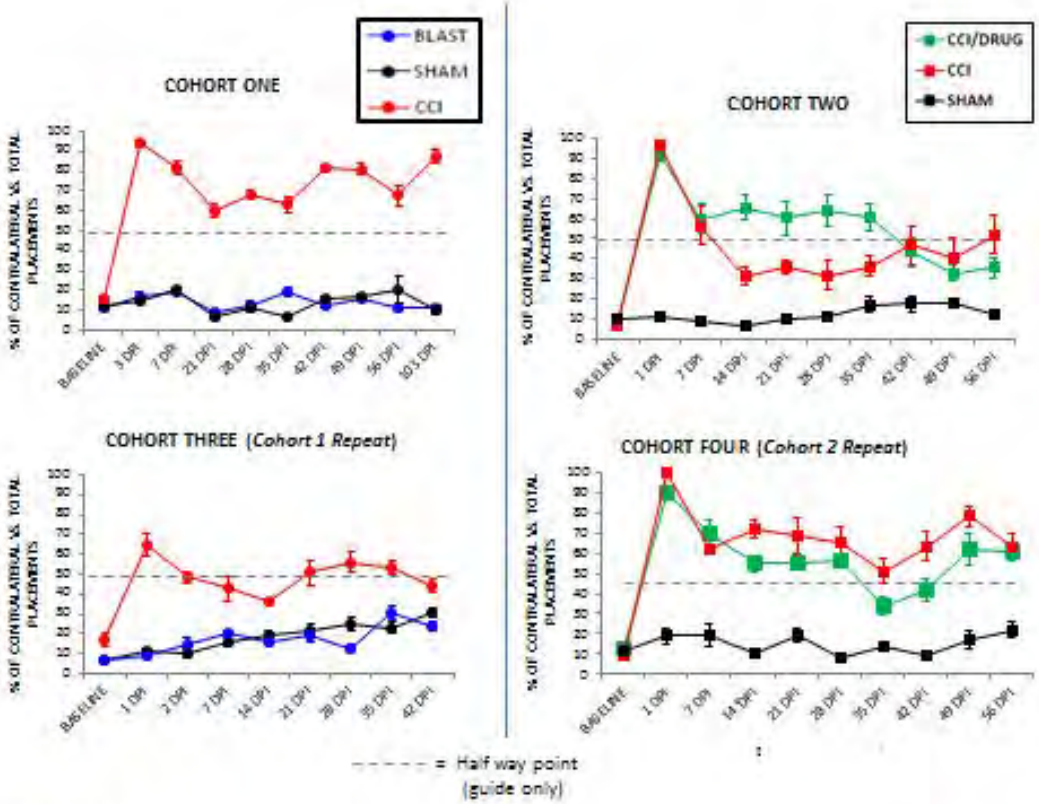
Dose response study: 22 Yorkshire males (38 - 42 kg); 5 groups (Sham (n=2), 0mg/kg (n=5), 1mg/kg (n=5), 3mg/kg (n=5) and 9mg/kg (n=5)). Veliparib given orally.

INJURY: CCIs were centered over the somatosensory region of the snout (10mm medial-lateral; 14 mm anterior-posterior). The injury was produced using a device built by the Bioengineering Department at the Medical College of Virginia with a 10mm impactor tip, at a velocity of 3.5m/second and dwell time of 400 m/sec.
HISTOLOGY: Iba-1 immunohistochemistry.
ANALYSIS: Iba-1 signal intensity assessed using ImageJ. One-Way ANOVA with Dunnetts post hoc test when appropriate.

REFERENCES:
HYDER AA, ET AL. (2007) [illegible]
IRVINE K-A, ET AL. (2010) [illegible]
IRVINE K-A, ET AL. (2014) [illegible]
D'AVILA JC, ET AL. (2012) [illegible]

FUNDING:
[illegible]
Dept. of Veterans Affairs

APPENDIX D


BLAST
SHAM
CCI
COHORT ONE
% OF CONTRALATERAL VS TOTAL PLACEMENTS
BASELINE
3 DPI
7 DPI
21 DPI
28 DPI
35 DPI
42 DPI
49 DPI
56 DPI
103 DPI
CCI/DRUG
CCI
SHAM
COHORT TWO
% OF CONTRALATERAL VS TOTAL PLACEMENTS
BASELINE
1 DPI
7 DPI
14 DPI
21 DPI
28 DPI
35 DPI
42 DPI
49 DPI
56 DPI
COHORT THREE (Cohort 1 Repeat)
% OF CONTRALATERAL VS TOTAL PLACEMENTS
BASELINE
1 DPI
2 DPI
7 DPI
14 DPI
21 DPI
28 DPI
35 DPI
42 DPI
COHORT FOUR (Cohort 2 Repeat)
% OF CONTRALATERAL VS TOTAL PLACEMENTS
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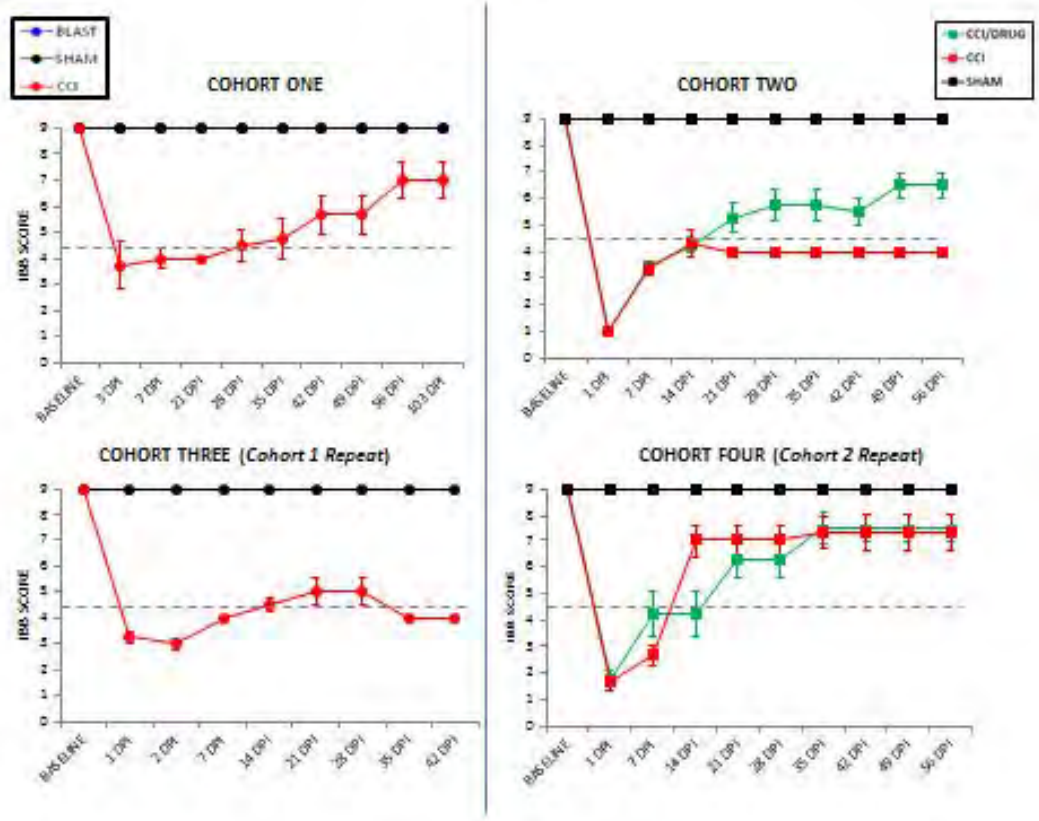
BLAST
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CCI/DRUG
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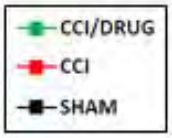
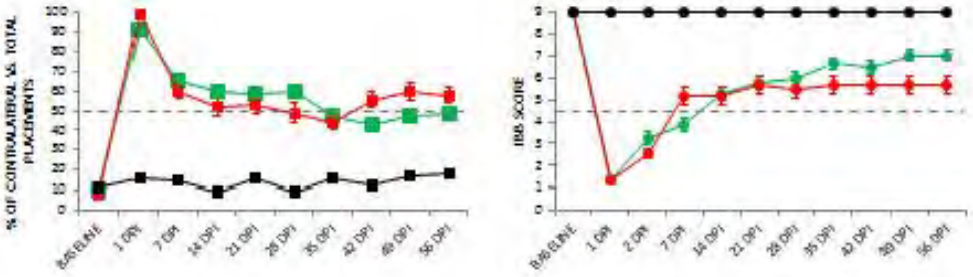
COMBINING COHORTS 2 AND 4

(VELIPARIB DRUG TRIALS)





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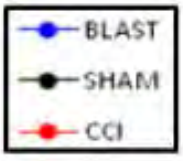
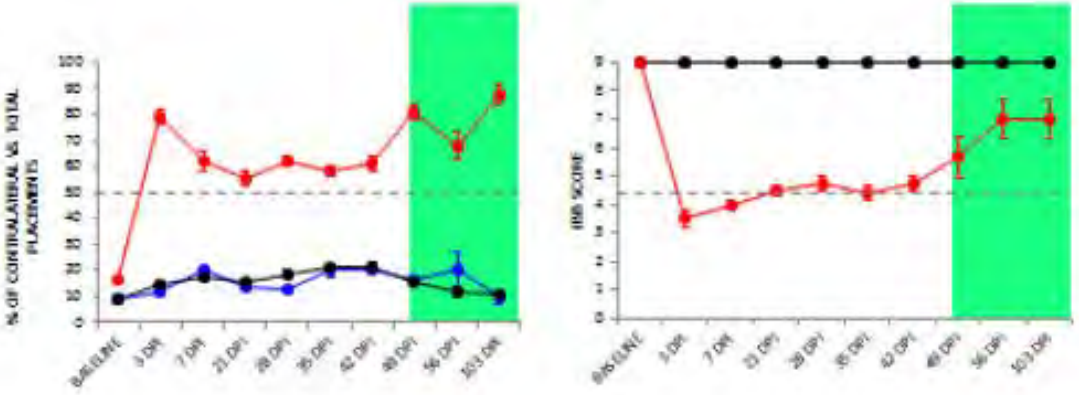
COMBINING COHORTS 1 AND 3

(BLAST TRIALS)





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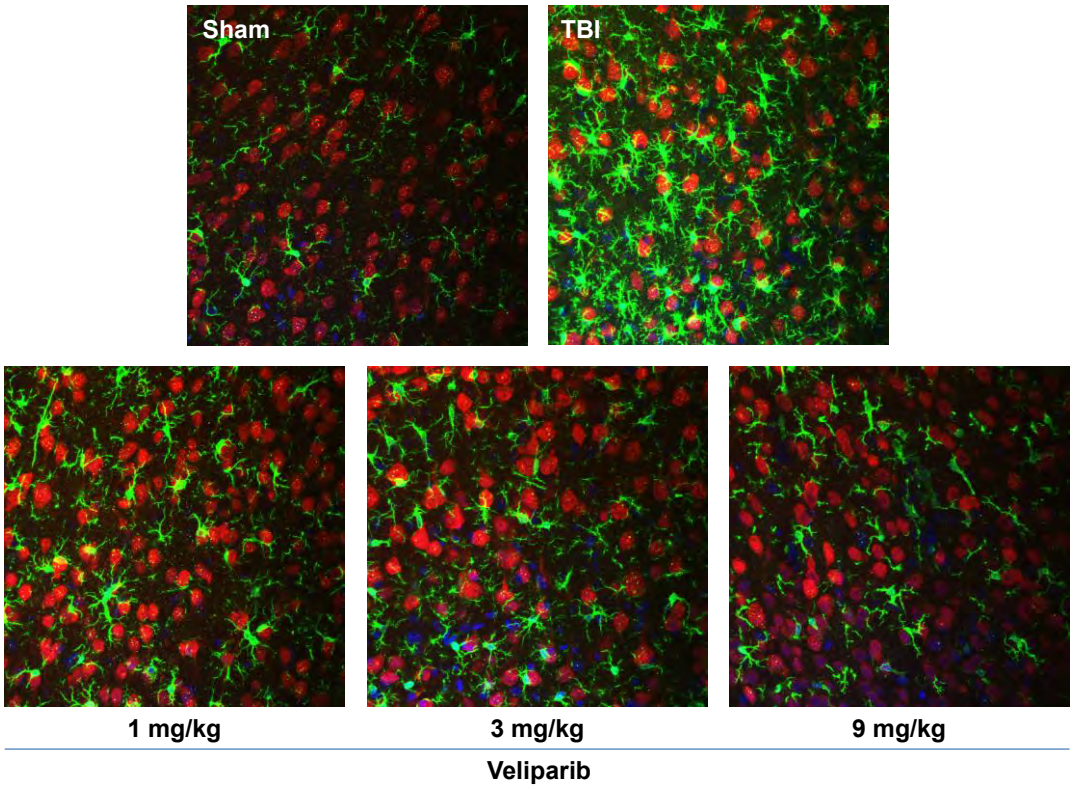
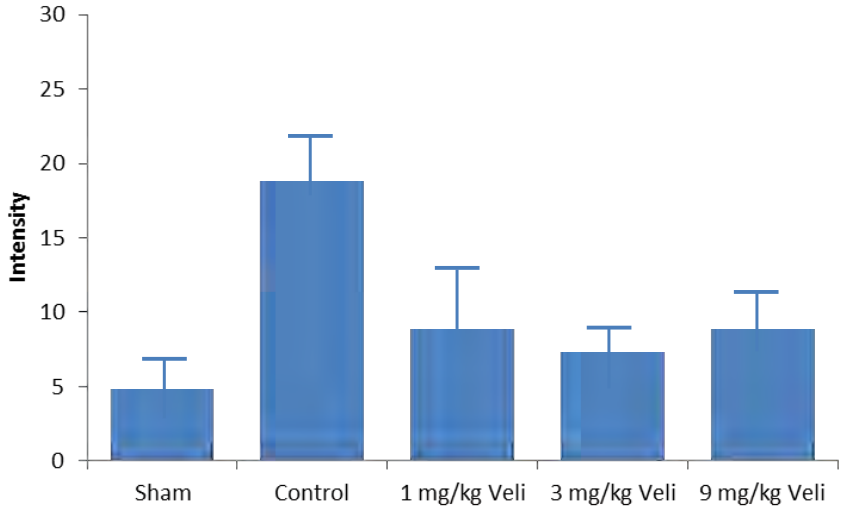
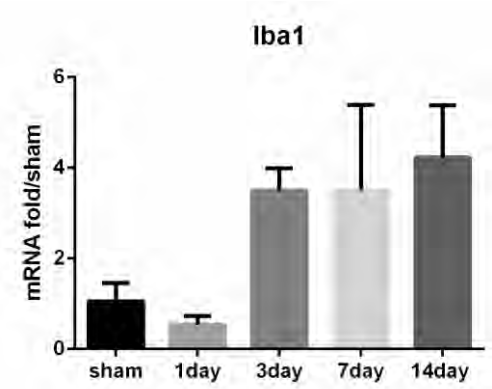
= COHORT 1 DATA ALONE

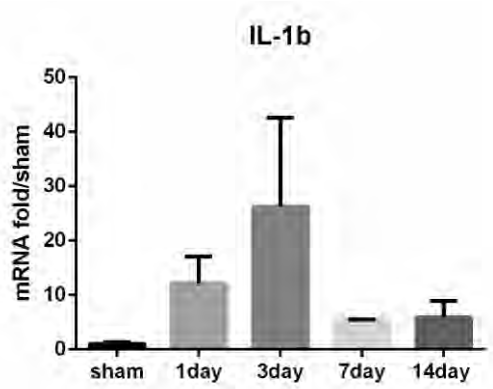
APPENDIX E

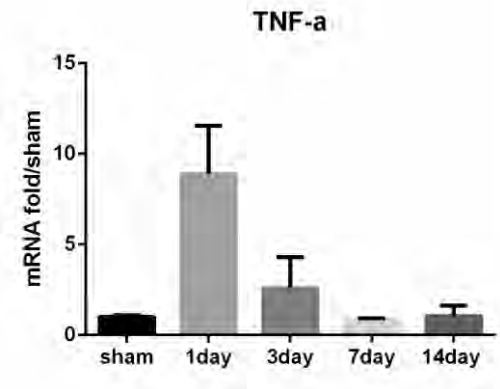

Sham
TBI
1 mg/kg
3 mg/kg
9 mg/kg
Veliparib

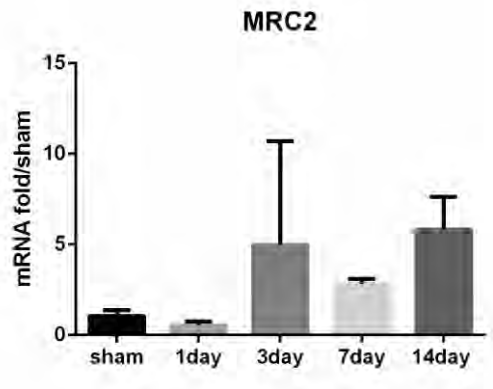

30
25
20
15
10
5
0
Intensity
Sham
Control
1 mg/kg Veli
3 mg/kg Veli
9 mg/kg Veli

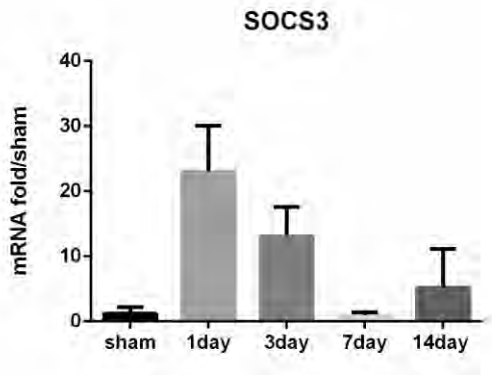
APPENDIX F

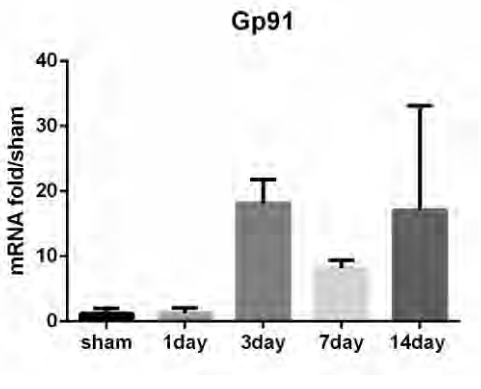


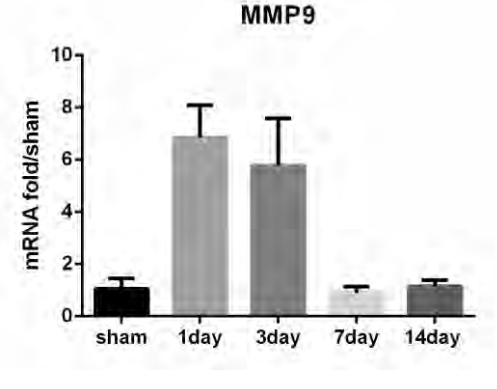




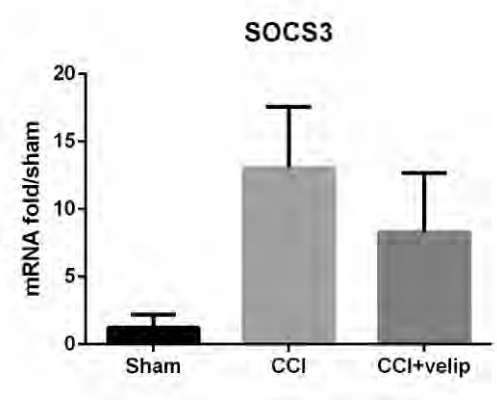


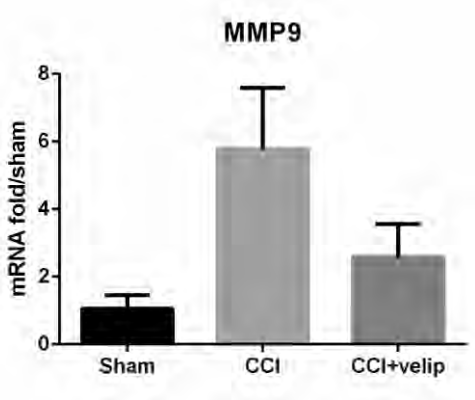


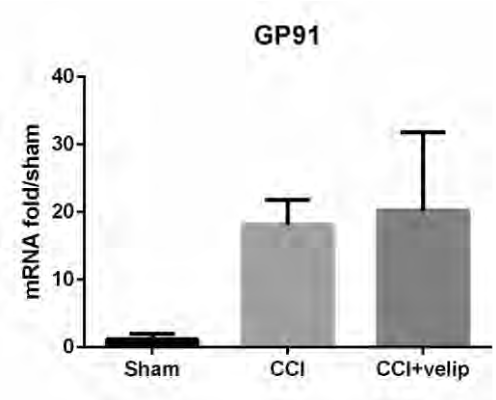




Gene expression in lesioned cortex after CCI in the rat







Effects of veliparib on gene expression at day 3 after CCI